REMARKS

Claims 1 and 3-27 are currently pending in the application. Claim 1 has been amended to more precisely define the standard dissolution test used to determine the *in vitro* release profile of the composition. Support for this amendment can be found in the application as filed, *e.g.*, at ¶ [0020] and in original claim 2, which has now been cancelled. Claims 26 and 27 have been withdrawn from consideration as being drawn to a non-elected invention. In view of the remarks below, Applicants respectfully request reconsideration and withdrawal of the rejections set forth in the May 29, 2008 Office Action.

Rejection Under 35 USC § 112

Claim 2 has been rejected under 35 USC § 112, ¶2 as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. In response, Applicants have cancelled claim 2, rendering this rejection moot. In addition, the amendment to claim 1 to define the standard dissolution test does not include the phrase "or a test substantially equivalent thereto." Accordingly, Applicants respectfully submit that the rejection is overcome.

Rejection For Alleged Double Patenting

In addition, Claims 1-16, and 18-25 have been provisionally rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over Claims 1-23 of co-pending Application Serial No. 10/626,166 ("the '166 Application"). Applicants have concurrently submitted a terminal disclaimer and therefore, respectfully submit that the rejection is overcome.

Rejection Under 35 USC § 103(a) Of Claims

Claims 1-25 have been rejected as allegedly being obvious under 35 U.S.C. §103(a) over United States Patent Application Publication No. 2002/0103240 to Pospisilik (hereinafter, "Pospisilik") in view of United States Patent No. 6,197,339 to Ju (hereinafter, "Ju"). For the reasons that follow, Applicants respectfully traverse the rejection.

The claims of the present application are directed to sustained-release dosage forms of pramipexole or a pharmaceutically-acceptable pramipexole salt (collectively referred to, hereinafter, as "***pramipexole***"), which provide therapeutically-effective plasma levels of

pramipexole over a period of at least 24 hours. The dosage forms also provide a specific *in vitro* dissolution or release profile.

Pramipexole is a drug that is, among other things, useful for the treatment of Parkinson's disease. The claimed sustained-release pramipexole dosage forms of the present application allow for oral doses of the drug to be taken only once a day, thereby providing a number of advantages over early versions of pramipexole (e.g., MIRAPEX®), including enhanced therapeutic results and better patient compliance.

Contrary to the assertions contained in the Office Action, the cited prior art fails to teach or suggest a once-daily dosage form of pramipexole. Rather, Pospisilik is directed to a process for the resolution of pramipexole into optically enriched or optically pure enantiomers. Pospisilik describes in detail the steps used to convert commercially-available pramipexole into its optically enriched form. Pospisilik, then alleges, in one brief paragraph, and in the broadest of terms, that "[c]ontrolled-release compositions may be produced using [the] pramipexole prepared by the process of the invention." *Pospisilik* at ¶ [0064]. Pospisilik contains no disclosure of the claimed *in vitro / in vivo* release profiles of the present invention, and contains no suggestion that its alleged controlled-release formulations are suitable for once-daily administration. Likewise, Ju, the other reference cited in the Office Action, fails to teach or suggest a once-daily dosage form of pramipexole. Indeed, Ju does not even disclose pramipexole formulations. Rather, Ju is directed to a sustained-release oral formulation of sumanirole; and in particular, a twice-daily formulation. *Ju*, at col. 3, lines 40-44.

In view of the differences between the claimed invention and the disclosures of the cited references, and as set forth more fully below, Applicants submit that a *prima facie* case of obviousness has not, and cannot be established and therefore, respectfully request reconsideration and withdrawal of the rejection.

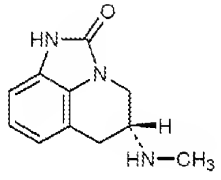
To establish a *prima facie* case of obviousness, three criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine the references. Second, there must be a reasonable expectation of success. Third, the prior art, when combined, must teach or suggest all of the claim limitations. Here, none of the criteria can be established.

I. Differences Between Pramipexole and Sumanirole Suggest A Lack Of Motivation In Ju To Make A Sustained-Release Formulation Of Pramipexole

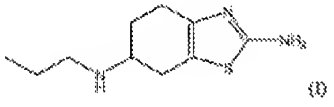
First, the Office Action has failed to show where in either of the cited references or in the knowledge generally available in the art there is a teaching, suggestion, or motivation to

combine the cited references. The Office Action asserts that motivation to combine Ju with Pospisilik exists because Ju allegedly teaches a sustained release form of sumanirole, which is a dopamine D_2 receptor agonist and is allegedly useful in the treatment of Parkinson's disease. *Office Action*, May 29, 2008, page 7. In response, Applicants respectfully point out the following: although sumanirole and pramipexole have shown utility in treating in Parkinson's disease, they have different properties in terms of chemical structure, and importantly, half-life, which would need to be taken into consideration by one of ordinary skill in the art when attempting to formulate either into a sustained-release dosage form.

Sumanirole is a D2 agonist of the following chemical structure:



Pramipexole is a D2/D3 agonist of the following chemical structure:



In addition, sumanirole has a relatively short half-life of about 3 to 5 hours; whereas pramipexole has a long half-life that ranges from about 9 hours for young persons to about 14 hours for elderly persons, depending upon the particular study. In this regard, drugs having a short half-life in plasma, due to rapid metabolism, excretion or other routes of depletion, are typically better suited for incorporation into sustained-release forms. Moreover, formulation of sustained release dosage forms is a highly individualized matter depending on the overall properties of the particular drug. Indeed, the following has been widely accepted:

> In this type of dosage form [i.e., sustained release], the design must be based primarily on the particular qualities of ***each individnal drug,*** especially as reflected in its biological performance. ***What may be an effective type of dosage form design for one drug simply is ineffective in promoting the sustained release of another drug*** because of the peculiar physical, chemical, and biological qualities of each individual drug substance. In order to maintain the constant level of drug in the system, the drug must be released from the dosage form at a rate that will replace the amount of drug

> being metabolized and excreted from the body. For ***each drug, this is a highly individualized quality***. In general, the ***drugs best suited for incorporation into a sustained release product are those having a fairly rapid rate of absorption and excretion***, those having relatively small doses, drugs that are uniformly absorbed from the gastrointestinal tract, and those drugs used in the treatment of chronic rather than acute conditions.

Ansel, *Introduction to Pharmaceutical Dosage Forms*, p. 170, Philadelphia: Lea & Febiger, 4th Ed. (1985) (attached hereto as Exhibit A). Accordingly, in the present situation, one of ordinary skill in the art would not reasonably expect two compounds with differing half-lives and different chemical structures to have similar effects in a sustained-release formulation. In view of these divergent properties, the two compounds would be expected to behave very differently in a sustained release formulation; thus, any knowledge gained by one skilled in the art from reading Ju's teaching of how to make sustained-release formulations of sumanirole could not be applied to pramipexole. Consequently, one skilled in the art would find no reason or motivation to combine the teaching of Ju with that of Pospisilik.

II. No Reasonable Expectation Of Success Existed To Make A Once-Daily Pramipexole Formulation.

With regard to the making of controlled-release formulations, it remains impossible to predict *a priori* whether a particular excipient will form an acceptably stable formulation with a given drug. Consequently, knowing how to make a sustained-release formulation of sumanirole in no way teaches, suggests, or motivates one skilled in the art to make a controlled-release formulation of pramipexole with any reasonable expectation of success. Therefore, Applicants respectfully submit that the Office Action incorrectly relies on Ju as motivation to make the claimed invention.

Likewise, Pospisilik's broad allegation that "[c]ontrolled-release compositions may be produced using [the] pramipexole prepared by the process of the invention," *Pospisilik* at ¶ [0064], in no way teaches, suggests or motivates one skilled in the art to make a once-daily pramipexole formulation with any reasonable expectation of success. In this regard, it is well-established that in order to render an invention unpatentable for obviousness, the prior art must be enabling. *In re Sujeet Kumar*, 418 F.3d 1361, 1368 (Fed. Cir. 2005). In effect, an invention is not possessed by the public absent some known or obvious way to make it. *In re Hoeksema*, 399 F.2d 269, 274 (CCPA 1968). Creating a once-daily, sustained-release dosage form of pramipexole required Applicants to undertake experimentation to understand its biological,

pharmacokinetic, and pharmacodynamic properties. Pospisilik does not teach or suggest how to make a once-daily pramipexole dosage form, nor does Pospisilik teach or suggest the release profile which is recited in claim 1. Applicants submit that just because Pospisilik may allege that controlled-release dosage forms "may be produced," it does not mean that one would be motivated by Pospisilik, with any reasonable expectation of success, to determine and obtain a viable once-daily, controlled-release profile of pramipexole. To make such a leap requires the level of experimentation and inventiveness present in the instant case.

The Office Action also contends that with regard to the rate of release, it is only a matter of dosing. *Office Action*, May 29, 2008, page 7. Applicants respectfully disagree. Applicants respectfully submit that the dosing factors recited in the Office Action, which are related to a patient's individual physical properties (i.e., weight, general physical condition, etc.), do not capture the scope of Applicants' research and experimentation completed to obtain a release profile for pramipexole. The limitation in claim 1 to a release profile is an unobvious inventive feature which permits control of dosing. In order to invent a controlled-release formulation for pramipexole, applicants undertook extensive experimentation to determine methods which reproducibly generate the release profiles claimed and exemplified in the specification. Nowhere in Pospisilik are these release profiles taught or suggested.

Applicants have invented a formulation having a unique release profile which causes specific, controlled-release dosing of pramipexole and provides the same overall drug exposure as immediate-release pramipexole (e.g., MIRAPEX®), while reducing the dosing from three-times per day, to once per day. Accordingly, applicants respectfully submit that there is no suggestion, teaching, or motivation in either Pospisilik or Ju (or in their combination), or any other basis in the knowledge generally available in the art, to arrive at the pending claims, nor is there any reasonable expectation of success absent extensive experimentation. Therefore, Applicants respectfully submit that claims 1-25 are patentable under 35 USC § 103(a), and respectfully request withdrawal of the rejection.

III. The Cited References, Even If Combined, Do Not Teach Or Suggest All The Claim Limitations As Required For A Prima Facie Case Of Obviousness.

A case of *prima facie* obviousness requires that the prior art reference (or references when combined) must teach or suggest all of the claim limitations. Applicants respectfully submit that this requirement has not been met since the Examiner has failed to show where in the prior art the following feature of pending claim 1 is taught or suggested;

> " . . . said composition exhibiting at least one of (a) an in vitro release profile wherein on average no more than about 20% of the pramipexole is dissolved within 2 hours after placement of the composition in a standard dissolution test; and (b) an in vivo pramipexole absorption profile following single dose oral administration to healthy adult humans wherein the time to reach a mean of 20% absorption is greater than about 2 hours and/or the time to reach a mean of 40% absorption is greater than about 4 hours."

As Applicants have already discussed above, the methods taught in Ju are inapplicable to making a sustained-release formulation of pramipexole because of the differences in half-life between pramipexole and sumanirole. Nevertheless, even if Ju could be combined with Pospisilik, Ju suggests creating a twice-daily controlled-release dosage form: "It is preferred that the daily dose be divided into two equal amounts since the sustained release tablet formulation adequately maintains blood levels when administered twice daily." *Ju* at col. 3, lines 40-44. Accordingly, even if combined, the cited art does not teach the claimed profiles following single dose administration. Because the cited art does not teach or suggest each of the claimed limitations, Applicants respectfully submit that a *prima facie* case of obviousness has not been established. Accordingly, Applicants respectfully request withdrawal of the rejection.

Conclusion

In view of the remarks above, Applicants respectfully submit that the pending claims are fully allowable, and solicit the issuance of a notice to such effect. If a telephone interview is deemed to be helpful to expedite the prosecution of the subject application, the Examiner is invited to contact applicants' undersigned attorneys at the telephone number provided.

The Commissioner is hereby authorized to charge any fees required or to credit any overpayment to Deposit Account No. 16-1445.

Respectfully submitted,

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